Pancreatic islet cell regeneration and growth. Introduction.

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INTRODUCTION

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This symposium, held in June 1991, was a gathering of international scientists to exchange their views on current concepts of cell growth and differentiation. Each scientist was asked to present a topic of their research related to cell growth and regeneration and to participate in a round table conference elaborating on current knowledge and sharing their experiences. By furthering this promising area of endeavor, a means of understanding ontogeny of cell development and of providing insights into tumor biology would prevail. Of prime importance was the anticipation that new information from a better understanding of the normal evolution of the pancreatic islet would generate alternative approaches to curing diabetes. This forward serves as a short introduction to the concept of pancreatic islet regeneration and the models currently in use to study the process.

DEVELOPMENTAL ORIGIN OF ISLETS DURING EMRYOGENESIS

The developing pancreas appears as a protrusion from the dorsal surface of the embryonic gut.[1] The different islet cell types appear sequentially during development *in vivo*. It therefore seems reasonable to propose that coordinated growth is dependent upon specificity of growth factors.

Islet cells *in vivo* also express several neuroectodermal antigens, for example, PGP 9.5,[2] neurone-specific enolase (NSE),[3] synaptophysin,[4] A2B5,[5] phenylethanolamine N-methyl-transferase (PNMT) and aromatic amino acid decarboxylase (AADC).[6] The endocrine cells of the GEP axis are capable of amine precursor uptake and decarboxylation and have, therefore, been given the acronym APUD.[7] The morphologic similarity of APUD cells suggested a common embryologic origin, which was believed to be the neural crest but later revised to include the neuroectoderm, or in the case of some of the endocrine cells, from the dorsal placoderm.

Studies by Ledouarin,[8] Pictet,[9] Andrew,[10] and their coworkers have cast doubt on this hypothesis, and most workers agree that these cells should be classified according to their secretory products, i.e., gastrin, somatostatin, glucagon. PP, etc. However, it is now thought that β-cells do not have APUD characteristics and are likely to be derived from gut, but express neuronal antigens such as the catecholamine biosynthetic enzyme tyrosine hydroxylase (TH).[11] The generally held belief that the neuronal characteristics of these cells indicated an ectodermal origin during mammalian embryogenesis has largely been dispelled.

During development *in vivo*, the phenotype of the mature islet cells appear sequentially. β-cells arise from progenitor cells localized in the pancreatic duct and these precursors transiently express TH while migrating away from the duct to populate a new islet. This suggests that the pancreatic duct is a source of endocrine stem cells throughout embryogenesis without the need to postulate a neuroendocrine origin. This notion is supported by the finding that the embryonic pancreatic duct *in vitro* is able to regenerate a new pancreas containing exocrine and endocrine cells expressing only peptides (mature cells), and cells containing both TH and a hormone (immature cells).[12,13]

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Teitelman has shown that pancreatic cells of endocrine origin can indeed express several neuronal antigens in addition to the peptide hormones.[11] She further showed that in the mouse embryo a primitive undifferentiated cell(s) led to sequential appearance of at least 4 different cell types containing either a hormone (e.g., glucagon), a catecholamine enzyme (tyrosine hydroxylase, TH) or combinations of these.[6] Under appropriate conditions these cells can be shown to differentiate into either neurites or adult endocrine cells. During regeneration, expression of neural antigens by developing cells was found to constitute an early phase to be replaced by the adult hormone secreting counterpart. Rosenberg and Vinik[14] have utilized a model for nesidioblastosis and shown that pancreatic ductal cells are capable of differentiating upon stimulation into adult endocrine cells capable of secreting insulin in a fully regulated manner.

ISLET CELL GROWTH AND DIFFERENTIATION

Factors which control the growth and functional maturation and differentiation of the human endocrine pancreas and gut during the fetal and post-natal periods are incompletely understood. The role of the fetal mesenchyme in epithelial cell development and differentiation appears to be important.[15-17] Possible mechanisms of action include: (i) secretion of an inducing or transforming hormonal growth factor, (ii) information exchange through cell-to-cell contact via paracrine and juxtacrine actions of locally elaborated growth factors, and (iii) production of an extracellular matrix rich in growth promoting factors. The soluble peptide growth factors are trophic substances that regulate both cell proliferation and differentiation and may be linked to islet growth.

One family of growth factors that may be implicated in islet growth are the somatomedins and their binding proteins. Insulin-like growth factors (IGFs) are important mediators of fetal and postnatal growth. Whereas these growth factors circulate (attached to binding proteins) they also act locally. Fetal rat islets release both IGF-I and IGF-II *in vitro* which may contribute to growth hormone-induced DNA synthesis.[18-21] It is apparent that the role of IGF-I, and the binding proteins, especially in the adult pancreas is far from clear. In this symposium Drs. LeRoith and Lauterio discuss aspects of IGF physiology, and LeRoith focuses upon differences in the role of the IGF's in regeneration of adult and fetal tissues. Dr. Hill emphasizes the role of the IGF's and their binding proteins in islet regeneration in the fetal pancreas at a time when the pancreas is susceptible to the influence of this particular group of growth factors. Dr. Bonner Weir also points out that in their model of islet regeneration after 90% pancreatectomy there is enhanced IGF gene expression in the ductules and certain connective tissue cells in contrast with the normal expression in capillary endothelial cells suggesting that IGFs may participate in the regeneration process after pancreatectomy in the rat.[22] Dr. Nielsen, however, contests the suggestion that the IGF's are important as pancreatic trophic factors and based upon his observations growth hormone itelf may be pertinent, at least in pregnancy, a state in which islet hypertrophy is found.

Several important glycoprotein components of extracellular matrix - the "integrins"- have also been recognized as playing a role in cell growth and differentiation. For example, fibronectin, laminin and tenascin.[23,24] Dr. Le Beau elaborates upon the role the integrins may play in cell regeneration. The role of these factors in the maintenance and replacement of a functional islet cell mass in the adult pancreas remains to be determined.

ISLET CELL PROLIFERATION IN THE POST-NATAL PERIOD

Several models designed to induce exocrine and endocrine pancreatic regeneration have been developed. In the model developed by Bonner-Weir and colleagues,[22,25] there is regeneration of both exocrine and endocrine tissue following a 90% pancreatectomy in which the increase in β–cell mass occurs as a result of the replication of existing β-cells and not necessarily because of a process of new islet formation.[22] This group have reported increased IGF-I mRNA production by capillary endothelial cells and proliferating ductules which may contribute to both endocrine and exocrine pancreas regeneration, but the precise

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Terazono et al developed a model in which 90% pancreatectomized rats or mice are treated with either nicotinamide, (a poly ADP-ribose synthetase inhibitor), or aurothioglucose resulting in exocrine and endocrine cell regeneration, and the appearance of a substance termed *reg* protein.[26,27] The gene encoding this protein has been termed the *reg* gene.[28] Human *reg* mRNA has been detected predominantly in the pancreas, and at lower levels in gastric mucosa and in the kidney.[29] *Reg* gene protein has also been found to be expressed ectopically in colon and rectal tumors,[29] linking enhanced *reg* expression to the transformed, proliferative state, at least for some cell types. Current evidence suggests that *reg* is expressed in acinar tissue and not regenerating islets. It may therefore be a paracrine growth factor. Dr. Okamoto, who pioneered the work on Reg gene and pancreatic regeneration, elaborates here upon his new findings. The controversy over the relevance of this growth factor in islet regeneration in other models is further discussed by Drs. Newgard and Rafaeloff.

Expression of an homologous gene, termed *rig*, has been identified in insulinoma tissue.[30] The significance of these genes remains to be determined. In both models of regeneration studied by Okamoto and colleagues,[26,27,29] islet size increased above normal over a period of weeks to months.

A second version of the 90% pancreatectomized rat model studied by Newgard and colleagues,[31] deals with *reg* expression in insulinoma-bearing New England Deaconess Hospital (NEDH) rats relative to normal controls and following tumor resection. They demonstrate that tumor implantation causes a sharp reduction in *reg* expression associated with a profound reduction in non-tumor islet size and that removal of the tumor, a maneuver that results in rapid β-cell proliferation, results in a large but transient induction in *reg* mRNA levels. Whether *reg* protein is β-cytotrophic is still an open question. The fact that high levels of *reg* mRNA are present in normal animals, in which β-cell replication is ongoing at a low, constitutive rate, are seemingly at odds with a growth-promoting role for this gene product.

Another model has been suggested by Dr. Sarvetnick[32] in which a regenerative process is observed in transgenic mice expressing Interferon-gamma in their pancreatic β-cells. These mice, in which diabetes ensues following immunodestruction of their β-cells, show duct cell proliferation and the appearance of more primitive neuroendocrine progenitor cells along the apical regions of the ducts. Dr. Sarvetnick discusses her most recent findings indicating that diabetes may not develop provided that the regenerative process outstrips the destructive process. This, we believe, is an important principle whereby an approach to induce regeneration may not be unreasonable in our quest for a cure for diabetes.

In 1982, we developed a unique model for islet regeneration in hamsters.[33,34] Hamsters 8 weeks of age are fertile, considered to be adult animals and respond better to the induction of cell proliferation than do older animals.[33,34] By producing partial obstruction of the hamster pancreatic duct by cellophane wrapping, new islet formation from ductal elements was observed. The mechanism by which partial obstruction in our model induces cell proliferation and differentiation is unknown. Using a parabiotic experimental design, these processes were shown to be mediated by paracrine and/or autocrine mechanisms.[30] Indeed, an extract prepared from a wrapped pancreas exhibited trophic activity when injected into other hamsters, but this was not observed when an extract prepared from a non-wrapped pancreas was administered. Drs. Rosenberg and Vinik review the data and the more recent developments in the use of a cytosol extract, containing the growth factor which we have called Ilotropin.

The presence of this specific growth factor, Ilotropin, in the β-cell cytosol extract has been hypothesized but the identity of the peptide had not been established. Dr. Pittenger reviews the current knowledge of the nature of the growth factor and the studies he has carried out to further define its characteristics. However, cellophane wrapping may initiate the release of a variety of growth factors that contribute to the coordinated, timely growth and differentiation of ductal cells. These possibilities and other factors that may be shared with factors important in the nervous system are highlighted by members of the faculty. The possible mechanism of action of the various factors as well as therapeutic applications are also discussed.

GROWTH FACTOR(S) AND NEOPLASIA

A great deal of interest is now being focused upon the factors responsible for initiation of growth, increase in cell number and size, differentiation into adult endocrine cells, growth cessation and cell maintenance.[36,37] The coincidental findings that the multiple endocrine neoplasia, type 1 syndrome (MEN-1) (combined occurrence of tum rs f the pituitary, pancreas and parathyroid glands) is associated with the loss of alleles on chromosome 11,[38,39] the same chromosome on which the insulin gene has been located;[40] the finding of parathyroid mitogenic activity in the plasma of patients with MEN-1;[36,37] and evidence that patients with MEN-1 might also secrete mitogenic factors for pancreatic islet-cells into plasma,[41] suggests a role for genetically determined circulating growth factors in the 'growth initiation' of these tumors.

It is apparent, therefore, that the conference was timeous and that the information pertinent to our appreciation of cell growth and differentiation is relevant to a possible cure for diabetes as well as a clearer understanding of factors that may be involved in pancreatic tumor formation. Conceptually, these conditions represent the two ends of a spectrum - diabetes with endocrine cell failure and endocrine neoplasia with unbridled cell growth.

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